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EXAMINER
O'DELL, DAVID K

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/783,848	DE BRABANDER ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,6-12,14,17 and 23-28* is/are pending in the application.

4a) Of the above claim(s) *14,17 and 24-28* is/are withdrawn from consideration.

5)☒ Claim(s) *3* is/are allowed.

6)☒ Claim(s) *6-12 and 23* is/are rejected.

7)☒ Claim(s) *23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 3, 6-12, 14, 17, 23-28 are pending are pending in the current application. Claims 14, 17, 24-28 are withdrawn from consideration and are drawn to a non-elected invention as per the requirement for restriction election. Claims 3, 6-12, 23 are under examination.

This application claims benefit of U.S. Provisional 60/448,851 filed on 02/20/2003. Claims 7-12, 23 are denied the right to priority of the provisional application. These claims are not supported by the disclosure of the provisional application.

Response to Applicant's Arguments

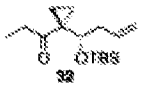
2. Applicant's arguments filed on February 14, 2008 have been fully considered but they are not fully persuasive. The rejections of the claims under 35 U.S.C. 101 are withdrawn in light of the affidavit by the applicant, however with respect to the 112 1st paragraph rejection for scope of enablement, the rejection is maintained. The applicant has argued successfully against the 101 rejection, he believes that the active conformation of Peloruside A is maintained in the (2-naphthyl)methylidene acetal and further that this conformation will maintain biological activity. While no data was actually provided, but rather it was stated that "Appendix B depicts the three-dimensional structure of peloruside A as determined by NMR studies." (presumably from the Jimenez-Barbero paper) it is unclear how this is relevant to a different compound. There is a reference to the Liao paper, which has some NOE data, however it would appear that these spectra were obtained in organic solvent. The conformation cannot be established on NOE data alone. Regardless the examiner will allow this particular acetal compound, since it was

at least prepared. There really is no clear answer as to whether it has biological activity and one could make an argument either way, despite the unsupported statements of the applicant, "These compounds are instead therapeutically active compounds in their own right.".

The primary outstanding issue is the scope of the claims. The applicant's incorrect in the statement that "the Examiner separately to reject claims 4-12 and 23 for lack of enablement, based primarily upon three synthetic challenges relating to the claimed compounds." This rejection was also based upon the how to use requirement of 112 1st paragraph, which will be taken up after a brief discussion of the how to make rejection. While the examiner agrees that at least some compounds outside the scope could be prepared. It is worth pointing out that the following statement is in error:

> Further, cyclopropyl ketone "B", which features a trimethylsilyl ether, is known as its *tert*-butyldimethylsilyl ether (32) in K.C. Nicolau *et al. Chem. Eur. J.* 3 (1997) 1957-1970 (copy enclosed).

Nicholau's compound 34 is an ethyl ketone.

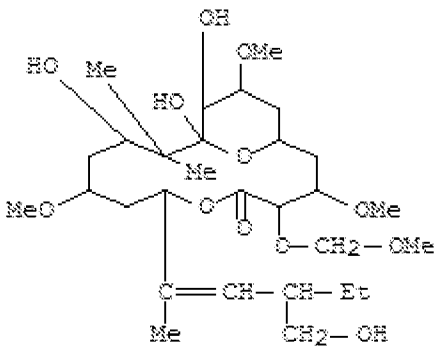


Compound B is actually a methyl ketone. Nonetheless we can see that most probably the selection of the protecting group was made for a reason. The examiner agrees that the regioselectivity of the dihydroxylation may be controllable.

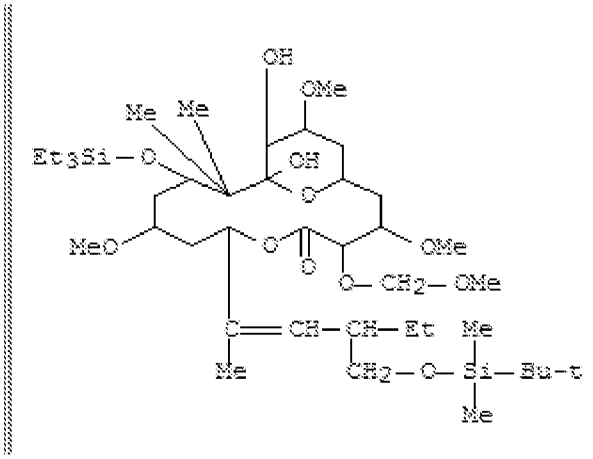
The examiner would like to point out that the skill level of the applicant is not the typical level of skill in the art. In fact it is clear that the applicant signing in the affidavit is more than just a routineer in the art. In fact it is immediately clear based on the CV submitted that the applicant is a genius in the art, as evidenced by the awards (NATO

fellowship, Fulbright-Hays Award, Sloan Foundation Fellowship) and numerous grants and publications. In order for an affidavit to be relevant to the determination of enablement it must be probative of the level of skill of the routineer in the art as of the time the applicant filed his application. See In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402, 406 (CCPA 1976).

The examiner does believe that some of the compounds outside of those exemplified could at least be prepared synthetically by a skilled artisan, however only a few compounds are exemplified. The MOM-protected Peloruside analog (which was allowed).



And several silyl protected compounds are all that support the instant claims:



Several compounds that were apparently tested have been identified as LX-3111 and LX-3136. The examiner is having great difficulty in identifying which compounds these actually are. While these materials are referenced in the Figures, no corresponding structure is assigned or revealed. The examiner requests clarification as to the identity of these materials. Perhaps these compounds were overlooked by the examiner. What compounds are these?

The paucity of working examples point to the key deficit in the disclosure, namely that undue experimentation would be required to practice the invention and the how to use requirement has not been met. While organic chemistry is highly unpredictable, the degree of unpredictability in the pharmaceutical art is even greater. As one reviewer stated, Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

> "….. compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.[15] In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure…(pg.

> 4536 column 2, line 9).....This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at ≥ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions) **(H).**

The examiner is not holding the applicant to a rigid scientific standard based in scientific fact, but rather the standard of patent law that the scope of the claims should be commensurate in scope with the invention disclosed. Claims 7-12 are entirely prophetic. The applicant has pointed to the Nicholau review to provide support for the prophetic choice of cyclopropyl in place of dimethyl:

> epothilones (K.C. Nicolau *et al. Angew. Chem. Int. Ed.* 37 (1998) 2014-2045). On page 2037, Scheme 38 details the construction of various epothilone libraries that interchangeably employ *gem*-dimethyl and cyclopropyl building blocks designated as compounds 31 and 216, respectively. That is to say, exactly the

The examiner submits that while such a modification to Peloruside A is an area that might be explored in future research, but it was not explored here. In fact making assumptions about modificaitons to Peloruside A that would lead to biological activity is based on specious scientific reasoning. Epothilones and Peloruside A while both tubulin polymerization inhibitors have different mechanisms of action and bind to different sites See Gaitonos et. al. "Peloruside A Does Not Bind to the Taxoid Site on β-Tubulin and Retains Its Activity in Multidrug-Resistant Cell Lines" CANCER RESEARCH August 1, 2004, 64, 5063–5067 and Hamel et. al. "Synergistic Effects of Peloruside A and Laulimalide with Taxoid Site Drugs, but Not with Each Other, on Tubulin Assembly." *Molecular Pharmacology* **2006**, *70*, 1555–1564, and also "The diverse actions of these drugs on microtubules are likely to produce different effects on mitotic spindle function, leading to different effects on cell cycle progression and cell killing." Manon T. Huizing

"Tubulin interacting agents" in Drugs Affecting Growth of Tumours Herbert M. Pinedo Carolien H. Smorenburg, Eds.; Birkhäuser Verlag: Basel, 2006 pg. 101-132 . Even between the canonical tubulin depolymerization inhibitors, Docetaxel and paclitaxel that are structurally very similar, the anti-cancer properties of such compounds may reside in mechanisms related to transcription regulation and each has distinct biochemical interactions with cellular targets:

"Tubulin polymers produced by two different tubulin promoters, Tau and MAP2, depolymerise at different rates and efficiencies in the presence of paclitaxel as compared with docetaxel, which suggests that the polymers generated by paclitaxel differ structurally from those generated by docetaxel [76]. Docetaxel does not alter the number of protofilaments in microtubules (13) like its naturally occurring taxane congener paclitaxel (12). Recent developments indicate that the antineoplastic activity of taxanes may originate in part from induction of genes encoding transcription factors with tumour suppressor effects as well as enzymes governing proliferation, apoptosis, inflammation, and other antiproliferative factors [81-83]." Huizig ibid. Pg. 110 (C) (E)

Again the examiner would like to point to the review on the chemical biology of epothilones provided by the applicant in the declaration (Nicholau et. al.). It is clear that a modest selection of derivatives of epothilones were made over many years by armies of chemists that are unarguably some of the most skilled in the world. Moreover, these derivatives clearly have very limited modifications to the macrocycle itself, and many limitations were revealed by detailed studies. See Altmann et. al. "Epothilones and related structures a new class of microtubule inhibitors with potent in vivo antitumor activity." *Biochimica et Biophysica Acta* **2000**, *1470*, M79-M91, the Figure 7 of Altmann is reproduced below:

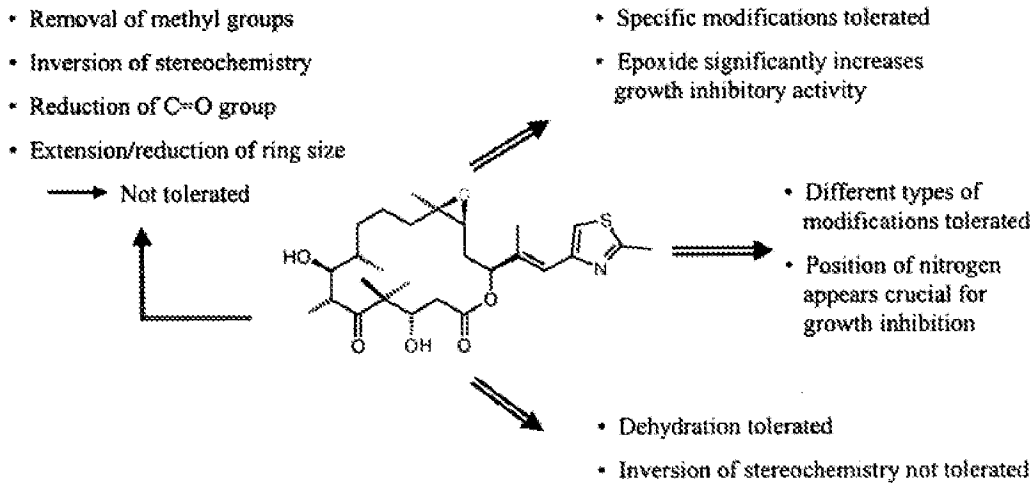


Fig. 7. Structure–activity relationships for epothilones.

The determination of these relationships and the discovery of potent analogs is a different invention, and one that the applicant has not shown to be in possession of. The specification does little but provide broad recitations of compounds that might be prepared and tested. While undoubtedly the applicant has provided a useful synthesis of Peloruside A, no trail is blazed to the derivatives. It is neither obvious nor predictable, to make such modifications.

In this case the claimed compounds bear no structural resemblance to the exemplified compounds, which are relatively homogenous and nonrepresentative of the scope claimed. In order to practice the full scope of the invention, one of ordinary skill would not only need to create synthetic procedures *de novo*, but also decide what compounds to prepare. The specification gives literally no guidance with regard to what the requirements for activity are i.e. which substituents would be preferred. See *Ex parte Herzog, Hershberg, and Coan*, 115 USPQ 195 (Bd. Pat. App. & Int. 1956) affirming the examiner, and stating "it becomes obvious that the expressions defining the organic acids

used.....are inclusive of inoperative materials and go far beyond the adequately disclosed subject matter of the specification." And also *Ex parte DIAMOND,* 123 USPQ 167 (Bd. Pat. App. & Int. 1959) where the examiner was affirmed for a scope of enablement rejection, and the court stated:

"the specification contains 23 specific examples, but it will be noted that they are to the preparation of relatively simple compounds.....This must be regarded as a relatively meagre and nonrepresentative disclosure to support claims which embrace millions of compounds. It should also be observed that appellant is working in a field where little prediction is possible and this Board has on several occasions held that the scope of claims should not be unduly extensive in fields where applicability is highly speculative or not explored and that subject matter which relies upon prediction for its support is unpatentable. Ex parte Middleton, 87 USPQ 57 ; Ex parte Kauck et al., 95 USPQ 197 , Ex parte Rosenkranz et al., Pat. No. 2,715,637. In Minnesota Mining and Mfg. Co. et al. v. Carborundum Co. et al., 155 F.2d 746, 69 USPQ 288 , the court held that 'An inventor cannot disclose a small number of components which will serve as a springboard for claiming an entire class.'"

In addition *In re Fouche* 169 USPQ 429 dealt with a similar issue with respect to how to use requirement of 112 1st paragraph,

"Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in In re Robins, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention. Nevertheless, an applicant must use some technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art. It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group."

See also: *Schering Corporation v. Gilbert et al.*, 68 USPQ 84 (2d Cir. 1946)

"Theoretically a multitude of substances not as yet found in nature and not as yet compounded could be synthesized, if skilled organic chemists were given the time and materials with which to work, and actually the formulas for them could be written. There is, however, a practical limit upon synthesis, though the extent of that is not fully known, for some of the new theoretical compounds might be impossible to create, and some

would be so unstable that they would disintegrate either at once or in short periods of varying length. Moreover, while analogy is at times useful, organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected."

And *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976)

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

In re Prutton, 96 USPQ 147 (C.C.P.A. 1952)

"The complete list of organic compositions includes, in generic form, most of the organic compounds found discussed in ordinary textbooks of organic chemistry..... It appears to be appellant's view that a selection of an unsaturated hydrocarbon from the first list and of a sulphide of phosphorus from the second list will provide support for the claims here under discussion. The Examiner holds, and properly we think, that the presentation of such lists from which reagents may be selected is not a sufficient disclosure to support claims to a particular class of reaction product which might be produced by proper selection of reagents and determining the conditions of reaction."

In re Walker, 22 USPQ (C.C.P.A. 1934)

"It is true, as argued by counsel, that appellant is entitled to claim not only the substance enumerated by him in his specification, but also their equivalents. However, in cases of this character, involving chemicals and chemical compounds, many of which of course differ radically in their properties, it must appear in the specification, either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that "the chemicals or chemical combinations included therein were generally capable of accomplishing the desired result." See *In re Ellis*, 37 App. D. C. 203; *In re Dosselman*, 37 App. D. C. 211; *In re Langmuir*, 20 C. C. P. A. (Patents) 733, 62 F. (2d) 93."

In Re Sus and Schaefer 134 USPQ 1962 301-310 (*affirmed*):

"It is, however, consistent with this public purpose embodied in the pertinent statutory requirement that the *invention claimed* shall be no broader than the *invention set forth* in the written description forming a part of the specification……thus it seems to us that one killed in this art would not be taught by written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only *certain aryl radicals* and certain specifically substituted aryl radicals would be suitable for such purposes." Emphasis in Original.

The examiner has more than made his case for the enablement rejection. The 112 2nd paragraph rejection is maintained for the reasons of record, and somewhat rephrased based upon the amendments. This action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 4-12, & 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention

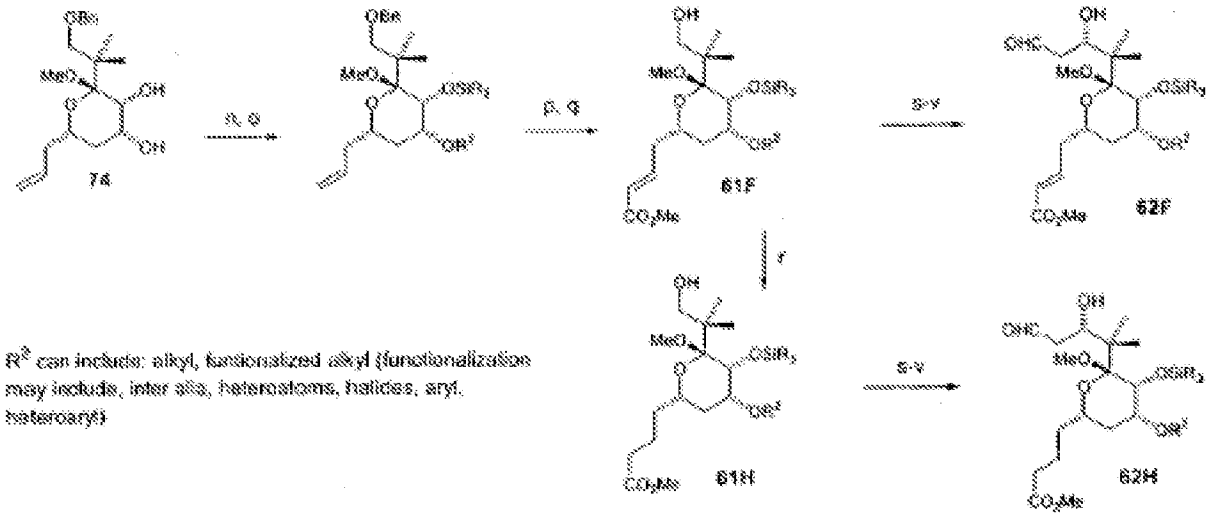
In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of heterocycles, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist/medicinal chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the

> initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)……..” Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention: Certain limitations of the chemistry used to prepare the examples, and the proposed prophetic examples is readily apparent. Claims 7-12, 23 have claims drawn to Peloruside compounds that lack the OR_4 or OR_6 moiety of structure 65D, claim 23, these are compounds like the olefin 65F & 65 E and the alkane 65G. However it is very clear that simply plugging in what are the analogous starting materials into the synthesis of Peloruside (which is the only example of the instant case) will not allow for their preparation. The prophetic reaction scheme of Figure 90 is illustrative of this clear failure. The olefin of compound 61F will be dihydroxylated and subsequently cleaved when treated with the conditions of s-v.



Reagents and conditions: n) base, R_2^8X; o) TESOTf, 2,6-lutidine; p) LiDBB, THF or Li, naphtalene, THF; q) Ru-alkylidene catalyst (cross metathesis); r) conjugate reduction; s) oxidation to aldehyde; t) allylBEt$_2$; u) cat. OsO_4, NMO; v) $Pb(OAc)_4$. PMB = p-methoxybenzyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LDA = lithium diisopropylamide, mCPBA = m-chloroperbenzoic acid, Bn = benzyl.

Figure 90

A more disturbing feature of the instant claims is the inclusion of a laundry list of Groups for R8, since R8 necessarily depends on the aldol reaction of ketones analogous to **6** with compound **23** in a key , however none of these reactions have been performed. Taking a closer look at the published account of this synthesis Liao et. al. "Total Synthesis and Absolute Configuration of the Novel Microtubule-Stabilizing Agent Peloruside A" *Angewandte Chemie International Edition* **2003**, *42*, 1648-1652, and comparing it side by side to the disclosure (shown on the next page) it is clear that prophetic synthesis or paper chemistry is far from straightforward and highly unpredictable.

Application Text

Peloruside analogs.

[0077] An example for the synthesis of analogs with C9-C 11 hydroxyls protected as a cyclic acetal is provided below. The biologically active forms of these analogs will have an enantiomeric relationship to the ones drawn in the schemes below. Union of fragments 6 and 25 and completion of a Peloruside analog is shown in Scheme 8 below. *Mukayama-type aldol reaction of aldehyde 25 with the enolsilane derived from methyl ketone 6 (BF3"Et20, CH2C12, -78°C) afforded almost exclusively (14:1) the 1,3-syn aldol product. This stereochemical outcome is contrary to the outcome expected from extensive literature precedents. Evidence provided below however, indicates that aldehyde 25 entered this reaction with an unprecedented bias for the formation of the 1,3-syn fl-hydroxy ketone 26 (80% yield). Hydroxy ketone 26 was protected as C13 methyl ether 27, followed by CBS reduction (and ester hydrolysis to reach seco-acid 28. Slow addition of this compound to a premixed solution of PPh3 and diisopropylazodicarboxylate* instigated formation of macrolactone 29 in 40-50% yield. *The stereochemistry of 29 was deduced based on a series of NOE correlations that locate H11, H13 and H15 on the same upper side of the macrolactone ring in agreement with the assigned C 13(S) configuration*. The synthesis of 29 provides an example of Peloruside spiroacetal analogs, i.e. Peloruside macrocycles that have the C9 and C 11 hydroxyl groups incorporated into an acetal ring, and can be prepared according to the general outline of Scheme 8. Note that enantiomeric 29, i.e. ent-29, and analogs will be biologically active.

Liao et. al.

With fragments 6 and 25 (derived from 24 as shown) at hand**, their union and completion of the peloruside macrocycle seemed an attainable goal, yet unexpected surprises lay ahead (Scheme 4).** *Mukaiyama-type aldol reaction of aldehyde 25 with the enol silane derived from methyl ketone 6 afforded almost exclusively (14:1) the compound that was assumed to be the expected 1,3-anti aldol product based on extensive literature precedent.[15] Evidence provided below, however, indicates that aldehyde 25 entered this reaction with an unprecedented bias for the formation of the 1,3-syn bhydroxy ketone 26 instead (80% yield). Initially unaware of this stereochemical outcome, we continued with methyl ether formation (!27), CBS reduction,[16] and ester hydrolysis to reach seco-acid 28. Slow addition of this compound to a premixed solution of PPh3 and diisopropylazodicarboxylate instigated formation of macrolactone 29 in 40–50% yield.[17]* We were able to deduce *the stereochemistry of 29 based on a series of NOE correlations that locate H11, H13, and H15 on the same upper side of the macrolactone ring in agreement with the assigned C13(S) configuration* (Figure 1). At this point, we were left with the obvious challenge of correcting the stereochemistry at C13. **Various attempts to remove the (2-naphthyl)methylidene acetal failed.[18] Undeterred, we embraced the opportunity to explore a more attractive avenue that would eliminate this protecting group problem altogether, that is, we decided to advance materials with a free C11 alcohol through the remainder of the synthesis.**

While the synthesis is one aspect, in this case these compounds bear no structural resemblance to one another when the acetals and "functionalized compounds are considered" and even if they did the situation is far from clear that they would have the desired activity. As one reviewer stated, Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

> "….. compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.[15] In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure…(pg. 4536 column 2, line 9)…..This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at ≥ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions)

In this instance we have no working examples for the majority of the claimed substituents and as stated by Jimenez-Barbero, J. et. al. " NMR Determination of the Bioactive Conformation of Peloruside A Bound To Microtubules" *Journal of the American Chemical Society* **2006**, 128, 8757-8765, conclusions pg. 8763 :

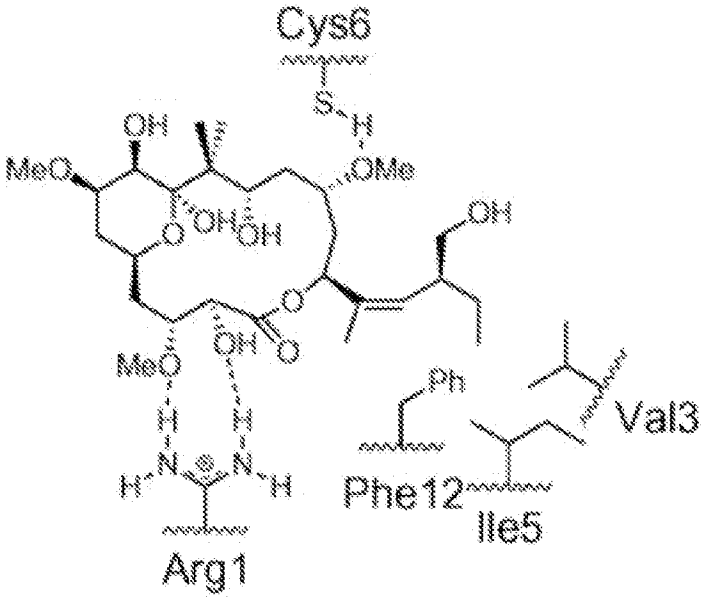
Nevertheless, despite the large size of the macrocyclic ring, intramolecular interactions within the Peloruside A ring strongly affects the conformational features of this molecule, which indeed only shows conformational mobility around a fairly narrow part of the molecule. **Specifically, van der Waals contacts and torsional constraints strongly bias its conformational behavior.** Yet, this existing conformational freedom, in thepresence of a given solvent, serves to modulate the presentation of polar and nonpolar surfaces to interact with the binding site. **Indeed, according to our experimental data, only one of the two major conformations existing in the water solution is bound to microtubules,** distinct from that predominantly present in nonpolar (chloroform) solvents. A model of the binding mode to tubulin has also been proposed, which involves the α-tubulin monomer, in contrast with taxol, which binds to the β-monomer.

I think no one would argue that the laundry list of "functionalized" compounds and "heteroaryls" would have the same activity.

Since few analogs of Peloruside A have been tested to date an analysis of the speculative biological activity of these compounds seems appropriate. The mechanism of action of Peloruside A is binding to tubulin at an unknown site, however the theoretical binding site(s) have been modeled and the conformation of the molecule is critical. See Jimenez-Barbero, J. et. al. "NMR Determination of the Bioactive Conformation of Peloruside A Bound To Microtubules" *Journal of the American Chemical Society* **2006**, 128, 8757-8765, conclusions pg. 8763.

Nevertheless, despite the large size of the macrocyclic ring, intramolecular interactions within the Peloruside A ring strongly affects the conformational features of this molecule, which indeed only shows conformational mobility around a fairly narrow part of the molecule. Specifically, van der Waals contacts and torsional constraints strongly bias its conformational behavior. Yet, this existing conformational freedom, in the presence of a given solvent, serves to modulate the presentation of polar and nonpolar surfaces to interact with the binding site. **Indeed, according to our experimental data, only one of the two major conformations existing in the water solution is bound to microtubules,** distinct from that predominantly present in nonpolar (chloroform) solvents. A model of the binding mode to tubulin has also been proposed, which involves the α-tubulin monomer, in contrast with taxol, which binds to the β-monomer.

Another author has proposed the following model for the interaction of Peloruside A with tubilin. Pineda, O. et. al. "Computational comparison of microtubule-stabilising agents laulimalide and peloruside with taxol and colchicines" *Bioorganic & Medicinal Chemistry Letters* **2004**, 4825–4829.



(b)

Thus the conformation of these molecules is critical for activity and in the instant case the compounds of the claims will have an unpredictable effect on the activity and may conformationally restrict the ring of Peloruside. The conformational is deemed critical by Jiminez-Barbero et. al. for the molecule to interact with tubulin. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

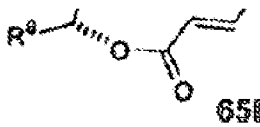
6. Claims 6-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "functionalized alkenyl" etc. is indefinite. Unless one knows what a substituent is a determination of what these compounds are cannot be made. The specification does not fully elaborate the identity of these substituents. This rejection is not being made for breadth, but for an inability to ascertain what this functionalization is. The claim amendments do nothing to overcome this rejection, but rather further obscure the definition:

wherein **each functionalized group is substituted with** ~~**the functional group is a heteroatom,**~~ a halide, an aryl, or a heteroaryl.

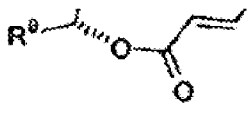
It now seems that the functionalized group is further substiuted.

Objections

7. Claim 23 is objected to for the following errors:



65E



65F , **Error! Objects cannot be created from editing field codes.** 65G,

It appears that some text was inadvertently added.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim 3 is allowed. Claims 14, 17, 24-28 are withdrawn from consideration and are drawn to a non-elected invention as per the requirement for restriction election. Claims 6-12, 23 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625